REMARKS

Introductory Comments:

Claims 33 and 73-79 were examined in the Office Action under reply and stand variously rejected under (1) 35 U.S.C. §112, second paragraph (claims 75-79); (2) 35 U.S.C. §112, first paragraph (claims 33 and 73-76); and (3) 35 U.S.C. §102(a) (claims 33 and 73-79). These rejections are respectfully traversed as discussed more fully below.

Overview of the Above Amendments:

All non-elected claims have been cancelled herein. Claims 33, 74 and 76 have also been cancelled. Claim 75 has been amended to read in independent format and incorporates recitations from cancelled claims 33 and 76. Additionally, extraneous language has been eliminated and the recitations regarding "first" and "second" polypeptides have been substituted with "first" and "second" polypeptide "domains." The dependant claims have been amended to track the language of claim 75.

New claims 80-86 have been added. Claims 80-85 recite polypeptide linkers. Claim 86 recites the protein of SEQ ID NO:6.

Support for the above amendments and new claims can be found throughout the specification at e.g., page 8, third full paragraph; page 9, second paragraph; page 23, second full paragraph; pages 29-30, bridging paragraph; page 46, first full paragraph; and Figure 1.

Cancellation and amendment of the claims is made without prejudice, without intent to abandon any originally claimed subject matter, and without intent to acquiesce in any rejection of record. Applicants expressly reserve the right to file one or more continuing applications hereof containing the canceled or unamended claims.

The specification has been amended to update the continuing information at page 1, as requested by the Examiner.

Rejections Under 35 U.S.C. §112, Second Paragraph:

Claims 75-79 were rejected under 35 U.S.C. §112, second paragraph as indefinite. The Office objects to the phrase "wherein the coding sequence encodes a first polypeptide." This phrase has been eliminated from the claims which now recite the presence of first and second polypeptide domains. Thus, this basis for rejection has been overcome and withdrawal thereof is respectfully requested.

Rejections Under 35 U.S.C. §112, First Paragraph:

Claims 33 and 73-76 were rejected under 35 U.S.C. §112, first paragraph as nonenabled. The Office notes the specification is enabling for an isolated polypeptide that binds c-erbB-2 comprising the 3 CDRs of 31-35, 50-66, 99-104 of SEQ ID NO:6 and the 3 CDRs of 157-167, 183-189, 222-230 of SEQ ID NO:6 (i.e., the protein recited in claim 77). However, the Office argues:

> The specification teaches the 520c9 single chain antibody of SEQ ID NO:6 and binds c-erbB-2 antigen (see page 46). The specification does not teach any other antibody with CDRs of 70% or 90% or antibodies that do not contain the full set of CDRs of SEQ ID NO:6 that bind c-erbB-2 antigen.
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> It is unlikely that antibodies as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of SEQ ID NO:6 in unspecified order, or CDRs that are 70% or 90% to those of SEQ ID NO:6 have the required binding function.

Office Action, pages 4-5. However, applicants respectfully submit the claims are indeed enabled.

In order to satisfy the enablement requirement, the specification need only set forth such information as is sufficient to allow one of ordinary skill in the art to make and use the invention. How such a teaching is accomplished, either by the use of illustrative examples or by broad terminology, is of no importance since a specification which teaches how to make and use the invention in terms which correspond in scope to the claims must be taken as complying with the first paragraph of §112 unless there is reason to doubt the objective truth of the statements relied upon therein for enabling support (*In*

re Marzocchi, 169 USPQ 367 (CCPA 1971)). Furthermore, a patent need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986) (citations omitted). Given the knowledge in the art at the time the application was filed, sufficient guidance is indeed present in the application to enable one of skill in the art to make and use the subject invention without undue experimentation, the standard by which compliance with the enablement requirement of 35 U.S.C. §112, first paragraph is measured. See, e.g., *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), quoting *In re Jackson*, 217 USPQ 804, 807 (Bd. App. 1982).

In particular, all of applicants' claims now recite the full complement of CDRs from SEQ ID NO:6. Additionally, all of the claims require the formation of a binding site for c-erbB-2. Thus, the only remaining concern of the Examiner's is with respect to the recitation of % sequence identity. However, sequences displaying at least 90% sequence identity to the specified CDRs are indeed believed to be fully enabled. In this regard, applicants set forth detailed methods throughout the application for making proteins as claimed. See, e.g., pages 26-30, 37-41 and the examples. Moreover, methods for producing proteins with 90% sequence identity to a reference sequence were well known in the art at the time the application was filed. For example, techniques for modifying sequences, such as site-directed mutagenesis, and the like, are described in, e.g., Sambrook et al., Molecular Cloning: A Laboratory Manual, Second Edition (1989); Kunkel, T.A. (1985) *Proc. Natl. Acad. Sci. USA* (1985) 82:448; Geisselsoder et al. (1987) *BioTechniques* 5:786; Zoller and Smith (1983) *Methods Enzymol.* 100:468; Dalbie-McFarland et al. (1982) *Proc. Natl. Acad. Sci USA* 79:6409. Using these methods, one of skill in the art could readily produce CDRs with at least 90% sequence identity to the reference sequence. Once obtained, the proteins could easily be tested for binding ability to c-erbB-2 using the methods detailed in the application. In particular, as explained at page 49, one method of purifying proteins is using a c-erbB-2 affinity column, thus resulting in a preparation of proteins that bind c-erbB-2. Moreover, the c-erbB-2 binding ability of the proteins can be tested in standard assays, such as described at page 54 of the

application.

The Examiner cites Rudikoff et al. and Colman as evidencing that substitutions in CDRs can affect binding function. However, as explained above, binding function is readily tested using routine methods typically utilized by the skilled artisan. Applicants remind the Examiner that a considerable amount of experimentation is permissible, if such experimentation is routine and/or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. MPEP §2164.01 states: "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." Accordingly, the recitation of "90% sequence identity" is believed to be fully enabled and this basis for rejection should be withdrawn.

Rejections Under 35 U.S.C. §102:

Claims 33 and 73-79 were rejected under 35 U.S.C. §102(a) as anticipated by PCT Publication No. WO 93/16185. This rejection is premised on the Office's assumption that applicants are not entitled to their original priority date of February 6, 1992. In particular, the Office acknowledges the present application claims priority from USSN 07/831,967. However, priority to the '967 application was not accorded because the application was not available for inspection by the Examiner. Accordingly, applicants are providing the Examiner with a copy of the '967 application as filed. As can be seen, the specification of the '967 application corresponds to the specification of PCT Publication WO 93/16185. Thus, the PCT publication is not properly citable prior art against the present claims and this basis for rejection should be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims define a patentable invention. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further written communications in this application to:

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Respectfully submitted,

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